THE CAUSES OF INFECTIOUS DISEASE.

THE WISH "to know the cause of things" is as old as mankind itself. In medicine the scientific period dawned at the moment when the question as to the connexion of disease with environment was clearly propounded by Diodorus and by Hippocrates, "the father of medicine."

In former times men were generally satisfied, and they are frequently satisfied to-day, with the vaguest conceptions of things, conceptions based on the common ground of a search after animate causes or personifications. Universal knowledge is plainly unattainable in a given section of time; hence men have always been forced to piece out in imagination part of the lacking facts,—that is to theorise; and the form such speculation takes on is naturally in accordance with the measure of cultivation prevailing at the time. Even now, as is clearly shown by a glance at the conceptions of image-worship among educated and uneducated individuals and peoples, there is for wide strata of society an imperative necessity for personification, for animate cause. Men abandon the idea of such animate causes only after more profound thought and arrive first at a mechanical, then at a monistic conception of the universe. Guided by the pervasive, all-embracing law of the conservation of energy, the exact sciences have everywhere struggled through to a mechanical and in part even to a monistic standpoint. The extraordinary complexity of the phenomena which confront us in the consideration of the origin of disease doubtless accounts for the fact that up to this time no one of the conceptions in medical theory,—either the dominant ones or those in direct conflict with the ruling conceptions,—have been freed altogether from the

old mystical animism. For this very reason not only do scientific periodicals resound daily with the clash of antagonistic principles, but the conflict is continued in the daily press and even in the conversations on the street corners.

In the presence of the great pestilence which the Greeks before Troy ascribed to the arrows of the offended god Apollo, Homer makes the father of gods and men say:

"Lo, how men blame the gods! From us, they say, spring troubles. But, through their own perversity, and more than is their due, they meet with sorrow."

This notion that pestilences are punishments for sins, and that they can be combated by sacrifices, prayers, and pilgrimages survives to-day in the midst of civilised Europe, an example of the deep-rooted proclivity in untrained minds toward a search after the animate, toward ontological speculation. The convenience of this ontological conception has given to the bacteria, in pure mockery of all scientific thought, an opportunity to celebrate their resurrection as the true disease-entities. Now, indeed, every sewing-girl knows that these good-for-nothing bacteria are the cause of *Seuchen*—which is the good German name for infectious diseases. Given the specific germ and the supposition is that we know everything needful; methods of fighting the disease, of disinfection and of healing are mere unimportant details. We cannot enough scorn those older physicians who knew nothing about bacteria, but who could not bring it into harmony with their better philosophic schooling that these things should be suddenly presented to them in pure cultures and in beautifully colored microscopic preparations, as the *cause* of disease. But in truth a sound kernel lay in their criticism. It was in a kindred spirit that Liebig ridiculed Pasteur, remarking *à propos* of Pasteur's view that the yeasts were the cause of alcoholic fermentation, that one could not see causes. Physicians, however, were not embarrassed by such considerations and, under the influence of Koch's ingenious methods, it became a pastime to show the causes of disease in pure cultures; their amusement

[1] The passage in question occurs in the Odyssey I., 32–34.—*Trans.*

flourished even in the drawing-room, and the phraseology of the new game became popular everywhere

We shall probably best reach a scientific understanding of the significance of bacteria in the origination of disease if we consider briefly the chief ideas hitherto held concerning disease. The conception, now generally embraced, of a "specific" infectious disease presents itself first in the writings of the great English physician, Sydenham. By this term is understood a sharply defined characteristic malady which, in uncomplicated and "typical" cases, is clearly distinguishable in its course and symptoms from other diseases: measles, smallpox, scarlet fever, malaria, pneumonia, and cholera are such "specific" infectious diseases. It was precisely this individuality of the "typical" cases that pointed to an individuality of origin, and in exactly this general sense Sydenham first compared "species of disease" with species of plants. For this physician, therefore, the "specific" disease itself was an "entity," it was personified. To have done away with this conception is one of the great services of Lotze and Virchow, who recognised more clearly than their predecessors that disease, as well as normal life, is a process. A process, a mechanical or dynamical process, cannot, however, be a living entity; and hence Lotze and Virchow struck a fatal blow at the unscientific notion of a disease essence. Something in addition to their notion, however, dwelt in the conception of Sydenham, namely the observation that the "specific" disease must have a cause, although he did not separate sufficiently the conception of predisposition to disease from that of cause of disease. He recognised further that the character of the specific infectious disease varies greatly in different epidemics, and called this variation *genius epidemicus*, without remarking that the term expressed a fundamental departure from his conception of rigid disease types.

From the manifest opposition between Sydenham's conception of a "disease species" as an essence and Lotze, and Virchow's conception of disease as a process we are able at once to understand Virchow's direct and vigorous opposition to those bacteriologists who still stick fast in the fetters of ontology, and for whom disease-

producing bacteria are only mystical entities which they would like to set in the place of the older personifications of priestcraft to be worshipped by devout physicians and laity.

Virchow, following up the process of disease as far as possible, came at last upon the diseased cells. Here he too fell into a singular error. He set up the diseased cell as the essence of disease, thereby substituting another entity for the one he had just thrown down. It was a weak place in the cellular pathology and one against which Virchow's opponents were of course quick to set themselves, without, however, giving due consideration to one point in his theory, namely, that he did not lose sight of the disease process in his contemplation of the diseased cells as the microscopic disease entities. He rightly conjectured that the something that appeared as disease must be something that was already preformed in the normal organism. As the cause is essential to its effect; so the production of disease requires an inward predisposition. Lotze had already expressed himself in a similar way.

For the normal processes of life the same principle had been known for a long time through the investigations of the German physiologists Haller, Reil, and Johannes Müller. Whatever be the outside forces that act, the eye perceives only light, the ear only sound, the glands simply secrete, and the muscles contract. It is therefore the internal conditions of the organism, of its organs, tissues or cells, that alone determine the character of the effect. The impulse that must come from outside to produce these effects is called the stimulus. Hence there must exist fundamental internal organisation, that is to say, a predisposition to something external. Since also, while the character of the stimulus varies, the physiological manifestations remain the same, the true cause of the manifestations must lie in this internal organisation. The intrinsic predisposition is physiologically the true and sufficient cause, and therefore the sole cause of the normal processes of life. On this point Virchow indeed recognised, in agreement with Brown, that a quantitative excess in the normal life stimulus is the cause of disease; too much light, for example, produces blindness. The effect of a stimulus may likewise be too great if the natural predisposition

be feeble, although the stimulus itself is still within physiological limits for a normal organism. Disease, then, may be regarded as the result produced by quantitative changes in normal conditions, either when the physiological organisation is too feeble or the stimulus too intense. Apparently, at least, infectious diseases which were presumed to be entirely new qualitatively scarcely fitted into this conception. The doctrine of the causation of infectious diseases is accordingly not indebted to Virchow for its furtherance nearly so much as are other realms of pathology.

On the other side, those investigators who were dissatisfied with Virchow's explanation fell into the opposite error in their own investigations. The Viennese doctor Plenciz had expounded very clearly and more fully than any one had done before him the doctrine, that the cause of disease must be sought in the existence and activities of minute specific living things. Afterwards Eisenmann and still more acutely Henle set forth this parasitic theory of infectious diseases, which grew then steadily stronger through important discoveries. In our own time, through the work of Davaine, Pasteur, Klebs, F. Cohn, J. Schröter, and Koch, it has become the prevailing theory. By the statement of this theory Henle was thrown into just as sharp opposition to Virchow as Koch has been recently, and at the time was forced by Virchow's want of consideration into other lines of activity, a fact that enables us to understand many personalities in current controversy. The now well-established parasitic theory of disease asserts that every "specific" infectious disease is caused by a "specifically" characteristic small living thing or microbe. Most of these microbes—but not all—belong to the group of bacteria. These bacteria, which are therefore wholly external entities, are, as Koch has set forth with great clearness, the sole true and sufficient cause of the infectious diseases. Differences in these diseases are due to differences in the small living things at the bottom of the process, in the disease-producing bacteria alone. In short, bacteria constitute the "entities" of infectious disease. According to the *theatrum diabolorum*, the view prevailed in the Middle Ages that "every sin is under the control of and operated by a particular devil"; at present each disease in

similar fashion has its own devil in the form of a specific bacillus. Beelzebub, the god of invisible evil flies, is peculiarly the protecting patron of the "specific" bacteriologists.

Between this conception—in respect to which the French daily press owns allegiance to Pasteur and the German to Koch—and the conception of Virchow, there exists a profound antagonism. It is the same conflict that prevailed between Liebig and Pasteur over the physiology of fermentation. Liebig sought the cause of fermentation, as Virchow did that of disease, in the internal constitution of the fermentable substances, while Pasteur conceived the cause to be the external and visible yeast-cells. This conflict of opinion is now still further complicated by Pettenkofer's theory that at least for certain diseases, such as typhoid fever and cholera, the determining cause or essence is to be found in the external conditions which vary according to time and place. Here we have put forth as the true and sufficient causes of epidemic disease three wholly dissimilar things, upheld by three different schools, and which are treated as "entities" or personifications. Virchow sees an internal cause in the diseased cells, his opponents see an external cause in the germs that bring about disease, and Pettenkofer sees a cause in the external conditions which play no particular rôle either in the eyes of Virchow or in those of Virchow's opponents. At the same time, however, it must be said that Virchow consistently attempts to break free from the personification idea and to arrive at the comprehension of processes.

I shall now attempt to show what is false in each of these conceptions and what is scientifically tenable, and in so doing I shall point out that all these investigators recognised a part of the truth, but that no one of them attained to a comprehension of the whole continuity of causes in the sense of modern exact science. I hope also to show that the existing antagonisms resolve themselves into a higher unity by means of which the solution of the problem becomes again surprisingly simple, a result quite common in cases where each such antagonistic principle is unduly inflated that it may redound to the glory of its school.

CAUSES AND THEIR IDENTITY AND EQUIVALENCE WITH EFFECTS.

While the modern investigator in the exact sciences holds the conception of cause and effect only in a unitary or monistic way, and while in epistemology there is a similar understanding of these terms, among the people at large the word cause connotes quite different meanings. Sometimes the word is used in the same sense as it is by the man of science; such a case is the recognition in reference to an explosion that the degree of destruction is dependent upon the kind and quantity of the explosive material. Sometimes, however, we characterise as the cause the spark or the electric current which precedes the explosion and evokes it. In the first case the cause is something internal and exactly concurrent with the effect, in the second case the cause is something external which neither qualitatively nor quantitatively stands in any sort of congruent relation with the effect. In order to eliminate this double sense of the word "cause" and to make an end of the confusion, a general agreement was reached in connexion with the discovery of the law of the conservation of energy by R. Mayer and his successors, and this has usually been conformed to in epistemology also.

If potential energy or the capacity for doing work is transformed into kinetic energy or actual work the two are equal in quantity. They pass over quantitatively into one another, and the work as effect accurately corresponds to and is measured by the capacity for work as cause. The true and sufficient cause of any effect is always something internal, something that follows from the kind and amount of the initial energy, from its quality and quantity alone and entirely. This is the conception of a cause,—*Ursache*—, an idea which the German language can express so exceedingly well while other languages must paraphrase it (in Latin, e. g., *causa prima* or *princeps*, to which the further definition *causa interna* and *vera* or *sufficiens* are necessary for completeness) in order to represent everything that the prefix *Ur* denotes to a German. It is the absolute thing "that exists behind all change and remains primordially the same" as Helmholtz expressed it. This alone we

now call cause,—*Ursache*,—both in the exact sciences and in epistemology, and we accept nothing but that conception as true and sufficient. Only what is provided for in the cause both in quality and quantity can appear as effect, and everything that appears as effect already exists in quality and quantity in the cause, that is in the internal organisation.

RESISTANCES AND EXTERNAL CONDITIONS.

In a strict sense causes may pass over of themselves, freely and spontaneously, into their effect, as when a thrown or lifted weight immediately falls. In practice, as a rule, this does not happen, since in order to render a definite work possible, we prevent the raised weight from immediately falling again by hanging it up by a cord or by placing a support under it. Such a resistance to the immediate conversion of potential energy into work may be removed in a given case easily or with difficulty, and a corresponding application of external energy is necessary in order to do away with the resistance and so bring about the actual fall of the weight just at the right moment. This resistance, as compared with the actual conversion of the capacity for work into work, is in itself something purely adventitious; the conversion comes about now easily, now with difficulty, now in this way, now in that, according to the given external conditions. When uncertainty existed about the connexion, therefore, the expression "occasional causes" used to be employed. Such modifying conditions are not necessary to the effect, they have not in themselves the character of true causes but they are practically important. Corresponding to every form of potential energy there exist by virtue of the external conditions, definite initial circumstances and kinds of resistance which determine whether a given form of potential energy, a given possibility of work, a given internal cause can be converted easily or with difficulty or not at all into kinetic energy, into work, into effect. So long therefore as the external conditions remain the same, the same form of potential energy must be convertible with the same ease into kinetic energy, the cause into the effect. If the conditions change then the transformation may take place more easily or with more difficulty or not

at all, since by altering the conditions the nature and amount of the resistance may be changed. This quantitative conception of conditions was first set forth by me at the Naturalists' Meeting in Nuremberg in 1893, and Mach at the same time showed that the constancy of conditions is full of significance likewise for the constancy of physical processes.

THE LIBERATION OF ENERGY.

If the conversion of cause into effect, of potential energy into kinetic energy is prevented by any sort of resistance, such conversion can obviously take place only if this resistance is removed. This process may be called, with R. Mayer, the liberation of energy, and the external forces which accomplish this are called liberating impulses. I have shown that we cannot content ourselves with neglecting these liberating impulses as of minimal amount, but that they are connected in a definite and quantitative way with the liberation of energy; the impulse must always introduce energy enough to overcome the resistance.

All changes of one form of energy into another are visible or invisible movements, and the impulses that set free the energy are likewise transmissions of a movement. Because of the continuity of energy, therefore, every form of liberated energy acts by the transmission of movement so as to set free other forms of energy. In the processes of disease external signs of this process are afforded in the succession of changing symptoms. The impulses that set free energy are something external, and under certain conditions may be altogether lacking; it is therefore at least redundant to speak of liberating causes.

We now know of course that small causes produce not great, but only small effects, whereas small impulses, when of sufficient power to overcome resistances, may set free great effects. The effect is always a process, not an essence, and the causes which alone produce the effect are internal. External conditions and external impulses are always links of unequal value in an endless chain in which a movement exists. Breaking the chain at any one point makes the production of the effect impossible.

It is in itself a matter of complete indifference what notation one adopts. I have myself decided upon a definite and unambiguous terminology and thus reached clear-cut and definite conceptions. Such a terminology is applicable in all realms of human science, and therefore makes an end once for all of the loose terminology which has been in vogue in medicine. When I presented this view at the Naturalists' Meeting in 1893, the objection was made from various sources that, in view of the slightness of the theoretical knowledge and scientific training possessed by the majority of physicians, my exposition was somewhat too recondite. I have tried to succeed now in making it sufficiently clear that in the exact sciences there is absolutely no place for the toys of ontology, for entities or for essences, but that we must deal with dynamic phenomena, with processes which interlock with one another. That, I trust, is the plain sense of my detailed exposition.

I now hope also to show in a way intelligible to my readers that even in the organic kingdom and especially as regards the doctrine of the origination of infectious disease we have no place for the "entities" of Sydenham's "specific disease," or of Virchow's diseased cells, or of Pettenkofer's determining circumstances of time and place, or of Pasteur's, Klebs's, F. Cohn's, and Koch's "specific" disease-producing bacteria. I hope further to show that, in considering the origination of infectious disease and the dynamic processes which are concerned, we can take account of all these things without degenerating into the mysticism of ontology. Although Behring rates it as one of Koch's services that he established the entity of disease by setting forth the bacteria as the specific cause, yet it is clear that in adopting such a conception scientific medicine would take a long step backwards. In such a confusing state of affairs a clear and unambiguous terminology has always been an advantage. This, however, some of my opponents who are adherents of the bacteriological ontology, did not seem to appreciate, because it is advantageous for this exploded theory to have a vague, ambiguous nomenclature. This is plainly in order that the advocates may be able to say, after each newly-won position of science, that they had always really meant something quite

different from what every reader of their works had previously supposed them to mean.

ATOMIC COMBINATIONS AND RESISTANCES.

When organic substances are built up out of the elements or out of very simple compounds, there always results as the product of such a synthesis not only an increased number of atoms in the molecule but an increased number of combinations of atoms. But the individual atoms are more firmly bound to one another in the very simple molecules that serve as a starting-point than they are in the complicated synthetic products. Carbonic acid and water, out of which starch and sugar are formed in plants, are simple molecules and the atoms in the molecule are firmly united as compared with the more complicated and more unstable molecules of starch and sugar formed out of the same atoms. Carbonic acid, water, sulphuretted hydrogen, ammonia, and nitric acid, all of which may enter into the synthesis of proteid are very simple, stable atomic compounds compared with the loose and complicated combinations in which these same atoms are bound in the proteid molecules. Along with an increase in the number of atoms in the molecule not only the number of atom-groupings increases, but generally also the looseness of combination. Conversely also, if a complicated and unstable molecule be broken down and fall to pieces into simpler and more stable compounds, the ease with which the breaking-down is accomplished and the number of possible new combinations must be in general dependent upon the complexity of the demolished molecule. In a molecule built up out of simple compounds there exists just as much energy or internal cause as has been expended in its construction. The manner, also, in which the atoms are grouped or bound together produces a definite resistance which may be overcome with more or less difficulty.

In these cases, therefore, the resistance bears a much closer relation to the store of potential energy than in most cases in inorganic nature; it is a direct consequence of the process of construction and therefore a property of the molecular structure. In the

structure and constitution of an organic body the total amount of energy which may manifest itself as effect exists as the potential energy of combination, as the internal cause. The kind of energy is prefigured also in the molecular structure, and so, finally, is the kind and amount of resistance which prevents the immediate and free transformation of cause into effect. I have explained the latter phenomenon briefly, as it is unnecessary to consider details in this place. The looser and more manifold the atom-grouping of a molecule is, the more energy the molecule contains; so much the less also is the energy needed to overcome the resistance and liberate the energy of the molecule, and so many more are the different kinds of external impulses which are able, by the application of anisochronous movements, to overcome the resistance, to convert the potential energy into kinetic, the cause into effect.

In purely inorganic processes the liberating impulses either bring about an effect or do not bring it about according to the extent to which they are quantitatively adapted for the removal of resistance. This property of the liberating impulses bears a relation to the quality of the potential energy set free only through the particular form of motion involved. In the liberation of the energy of complex organic molecules, on the other hand, the impulses bear more of a qualitative relation. But whether they can or cannot make themselves felt in such a qualitative way again depends in the last instance exclusively upon the character of the molecular structure. The nature and amount of resistance depend also upon the structure, that is to say, upon the internal organisation of the organic substance upon which a liberating impulse impinges. Resistance is therefore in plain terms a result of adaptation, while in the inorganic realm it often results from the simple juxtaposition of different processes and their reciprocal action.

Accordingly, in our inquiry into the causes of organic processes we meet everything that we find in inorganic processes but better regulated and more intricate, in the first place by means of adaptation, and secondly, because of the complexity of the phenomena. We find various forms of potential energy or internal causes which may be transformed into kinetic energy, into work or

into effect. The effect, so far as its special features are concerned, depends solely upon the qualitative character of the compound, that is to say, the mode of union of the atoms in the molecule. This qualitative relation is more striking in the realm of the organic than in the inorganic, where it has been recognised from R. Mayer to Hertz that the qualitative relations may be overridden. At bottom, however, exactly the same subjective limits wall us in, although that is a fact that need not be dwelt upon here. Every quality is of course from one point of view a sort of sense-illusion or sense-limit, and not anything truly objective. We find forms of resistance, then, which result from characteristics of structure and therefore present not only the well-known quantitative but also a qualitative side worthy of consideration.

Finally we need to consider the liberating impulses which quantitatively and qualitatively serve to remove the resistance. We now depict the problem in a somewhat different way, because in the historical development of the subject the aspect of quality so predominated that the quantitative side was wholly overlooked or not recognised, and only Liebig, Lotze, Virchow, and Nägeli suspected the existence and partly recognised single factors of this kind.

The fact that a long time elapsed before, in the natural sciences, the dualistic contrast between organic and inorganic was abandoned is connected with the fact that the conceptions of the *Critique* so long lingered in men's minds. Kant was a dualist, and for him inorganic processes were the consequences of necessity; organic processes, of purposiveness. Schopenhauer found quantities in inorganic processes, qualities or stimuli in organic. Unfortunately dualism in the latter form still haunts the minds of many physicians who often never suspect its retrogressive character as compared with the mechanical and monistic point of view.

PREDISPOSITION TO DISEASE ACQUIRED AND INHERITED.

As the result of inheritance, individual development, and adaptation to existing conditions of life, every man,—and man is the subject I place from now on in the foreground,—possesses in his entire

organism, in his organs, tissues, cells, and body-fluids, at a given time and place, a definite kind and amount of potential energy or cause. This, when it becomes manifest, we designate variously as a physiological property or irritability, as a morbid susceptibility, as a predisposition to disease or as immunity. A predisposition to certain diseases exists among different races and species. Negroes for example are infected with smallpox much more easily than Europeans, while the latter sicken more easily with yellow-fever and the disease assumes in them a more fatal character. A varying susceptibility to disease is found among individuals of the same species, as is established by the fact that among our population only 3 to 7 per cent. contract cholera, the rest of the population resisting the disease. In spite of the ample opportunities of infection with tuberculosis which are afforded every one, only some 20 to 25 per cent. of the population really contract any form of the disease. Indeed, if we consider the most dreaded of all known infectious diseases, the Black Death of the Middle Ages, we are told that only one fourth of the whole population of Europe contracted the disease, some 75 per cent., therefore, being naturally protected, while it is reported that the small-pox in Central America destroyed one-half of the native inhabitants.

That the different organs of the body possess a varying predisposition to disease may be inferred from the fact that diseases which are now known to be infectious were once regarded as organic, as, for instance, inflammation of the lungs and catarrh of the intestine. The striking differences shown in the organs attacked by tuberculosis, and the selection of different organs at different periods of life beautifully illustrates this point. The experience of physicians and the vast material placed at our disposal in statistics of disease and death have, in short, shown the existence of a predisposition to disease and have made it clear that susceptibility to different diseases varies greatly according to the period of life and again according to sex.

Plant parasites furnish some fine examples of predisposition. *Laboulbenia muscæ* is found only in the house-fly. *Cordyceps*, on the other hand, occurs in the larvæ of different butterflies and other

insects. *Phytophtora infestans* occurs only upon potatoes, while *Phytophtora omnivora* attacks a number of other plants but not potatoes. Species of moulds of the genera *Pythium* and *Sclerotinia* attack only plants that are young and rich in water and therefore less resistant, but do not attack the older plants which are less rich in water. *Cystopus candidus*, according to De Bary, causes the white rust of the garden-cress (*Lepidium sativum*); in fact all plants are susceptible to the attack of this fungus, but only when they are in the cotyledon stage; when the cotyledon falls off the leaf becomes resistant and the spores and germ-tubes of *Cystopus* penetrate only locally in every case, without being able to penetrate far into the interior. The blister-rust of spruce needles occurs according to Cramer in its other parasitic forms only upon the leaves of the Alpine-rose and wild rosemary, *Chrysomyxa rhododendri* and *ledi*. In localities where these two plants do not occur no blister-rust is found upon the spruce. Similar relations exist, according to De Bary, between the rust of wheat and the Aecidia of the barberry. The "local" disposition is therefore, in reality, a disposition of the host. According to De Bary, if the disease predisposition due to the host be removed—e. g., if the barberry bush be banished to a distance—the disease disappears, and again arises when susceptible host-plants are introduced.

Perhaps the most remarkable fact in this connexion is that very definite predispositions may be acquired. An attack of the affections due to "catching cold" or of rheumatism—affections causally related perhaps—increases the tendency to those diseases, while an attack of any one of the more acute infectious diseases, such as smallpox, scarlet fever, or measles, confers immunity against another attack. Susceptibility to disease has become protection against it. Such an individually acquired immunity can be transmitted from mother to child. I shall not in this place broach the much mooted question, whether or not acquired characters can be inherited, and shall not try to set forth here how, upon the basis of my representation of the problem of causation, the question really comes within our reach. It may suffice at present to make clear that, under certain circumstances acquired characters, among which

may be reckoned acquired tendency to disease or acquired immunity, must be inherited. According to Kaltenbach, twin-sisters, originating from two different ova—double placenta from two choria—were exposed in equal measure to infection from scarlet fever: one of them remained entirely immune, the other succumbed immediately. The latter resembled the father, the immune child the mother, who, fourteen months previously had experienced a severe attack of scarlet fever. Here was a pronounced inborn quality, but this quality was inherited and the character thus transmitted was acquired by disease. An interesting observation has been made in certain cases of twins and triplets. When, by infection of the mother with smallpox opportunity was given for placental, intra-uterine infection of all the offspring, one or another of the children remained free from the disease, and the possibility of infection taking place by means of the placenta was proved by its occurrence in the case of one or more of the children. But it has also been observed that a pregnant woman who had been successfully vaccinated gave birth to a healthy child who nevertheless sickened three years later with smallpox, and in another case that smallpox was observed in a fœtus whose mother had previously suffered with the disease. Whether an acquired disposition is transmissible depends upon the kind and duration of the influence. On this point it is easy to deceive oneself. In Ehrlich's experiments upon rendering animals resistant to poisons, at first sight it seemed as if the young inherited immunity; another interpretation proved, however, to be the true one. The young of a non-resistant mother, when fed on the milk of an immunised mother, acquired immunity, thereby showing that the immunity was not conferred by inheritance. It was instead an instance of extra-uterine, individual immunisation by means of the protective substances contained in the milk of an immune mother or nurse. According to Tizzoni, however, immunity to tetanus acquired by the father can be transmitted to the offspring.

The existence of a definite predisposition to disease—as well as its opposite—is dependent upon inherited traits and upon adaptation to the conditions of existence, among which may be num-

bered not only soil, water, air, and the general relation of weather and climate, but also social conditions. These changing circumstances or external conditions act upon the internal disposition which remains always the same. If these conditions change, then adjustment must occur, that is, changes in the internal constitution must take place. Every change in locality, every considerable change in nutrition may, therefore, make itself felt upon our predisposition. By utilising the information gained from experiments in this line we have a means of influencing the disposition in our favor, or, for instance, by removal of social mal-adjustments, by improvement of the locality in which we dwell by changes in metabolism through introduction of better nutriment, or by regulating the temperature conditions of the body. Finally we are able to make use of the fact that in the act of undergoing a disease the predisposition to that disease is removed and converted into its opposite, immunity.

In no case can anything appear in the form of disease which was not previously present in the body as a predisposition; external forces are able merely to make this predisposition apparent. It is therefore at the outset important to hold fast to the fact that we are in a position to act upon a given disposition by a whole series of changes in external conditions; we can heighten it or remove it. Herein lies also the reconciliation of the physician's art, which has reference to the individual, with the official health regulations, which have regard to the conditions making for the betterment of all. When the physician, by thorough observation and investigation, knows the conditions that influence a given disposition in a definite way, when he is scientifically trained and has a true conception of hygiene and is at once physician and naturalist, then he is able to cure disease by use of the very same forces which serve to create or alter the human constitution. In this simple sense there is a true art of healing.

The external conditions to which a human being is subjected according to season and locality make themselves felt throughout the organs, tissues, and cells of the whole body. This they do through the mediation of metabolism and by the aid of the nervous

system, factors that determine the character of the synthesis or the building up of the organism, and as before mentioned, that determine also the kind and amount of the resistances to release of energy. We are accordingly set the further task of guiding the course of events by the use of those conditions that create resistances, and guiding them further in such a way that the physiological resistances are easily overcome, and the liberation of energy follows easily and in normal paths, while pathological resistances are avoided and the pathological setting-free of energy cannot result. Since the kind and amount of resistance met with in the organic kingdom is a consequence of organic structure, this task practically coincides with the first, namely that of influencing with the help of suitable external conditions the potential energy, the cause, in a word, the disposition of men.

DISEASE-STIMULI AND DISEASE-EXCITANTS.

The liberating impulses, as they are called in the inorganic sciences, are called stimuli in speaking of normal life-processes. Liebig, in treating of fermentation processes, first used the term excitation, so that we may speak of the stimuli that evoke disease as excitants of disease.

Through a depression of the physiological organisation and a consequent lowering of resistance, normal physiological stimuli may become disease stimuli, or, the organisation and resistance remaining the same, the normal stimulus may become more intense and be converted into a disease stimulus; in other words, the stimulus may come into play only quantitatively. If this be so, it is easy to understand how the kind of effect which we call disease depends qualitatively upon the kind of organ, tissue, or cell concerned, and indeed solely upon these and their internal adjustments (Virchow). If the disease stimulus, however, is a living thing, then, according to Koch's conception, the natural law should be summarily abolished and the quality of the disease stimulus, namely, the kind of disease-producing bacteria, should determine the disease, in other words, bring about the effect. We get only apparent support for this view from such facts as that anthrax bac-

teria always evoke anthrax, and tubercle bacilli tuberculosis in susceptible animals, and that many diseases, such as malaria and pneumonia, have a typical and often cyclical course. If the facts are considered attentively, they reveal a state of affairs really quite different. If we suppose that the pathogenic bacteria are "specific entities," that they are really the true and sufficient cause of disease as Pasteur and Koch have affirmed, then at least four conditions would have to be fulfilled. First, the disease-producing bacteria should exert no other effect than that of producing disease; second, their ability to produce disease should remain constant; third, they should affect all animals in the same way without reference to particular species; and fourth, they should produce only a single, sharply defined, typical and "specific" infectious disease. In such a way as this Koch has really pictured things to himself,—this is indeed the leading motive of his school,—while Pasteur who also originally looked upon the question in the same way, later adopted other opinions. The dogma of the "specificity" of the minute organisms that excite disease, the belief in the existence of pathogenetic or pathogenic bacteria, meaning thereby belief in unvarying specific character and physiological effect, was especially developed by Henle and later was worked out by Davaine, Pasteur, J. Schröter, F. Cohn, Klebs, and Koch. Other investigators, among whom I need name only Nägeli and Billroth as the leaders, have believed, in opposition to this view, that bacteria are constant neither in kind nor in action.

Now in the first place, are disease-producing bacteria capable of producing any other effect? By the modern method of pure cultures it has been established beyond all doubt that disease-producing bacteria do indeed display other activities; the successful culture of pathogenic bacteria is in itself a proof that those bacteria are not restricted to a parasitic existence and to the exciting of disease. Thus for example the bacteria of glanders develop a brown pigment upon potato; the cholera bacteria form a yellow or brown pigment upon potato, and in sugar solutions cause an acid fermentation; the so-called golden pus cocci, which are the most common pyogenic bacteria, form in cultures a splendid yellow pigment and

in sugar solutions produce acid. Whereas formerly, in accordance with F. Cohn's view, bacteria were distinguished according to their "specific" activities and characters into disease-producing or pathogenic, fermentation-causing or zymogenic, and pigment-forming or chromogenic, the foregoing examples show that a single bacterial species, a single "specific" minute living thing is capable of exercising all three of the specific activities formerly held to be essentially distinct. The "specific" bacteria are therefore not the true cause; that lies in the character of the nutrient medium; the bacteria can elicit only what is preformed in the structure of the medium. I have given the name of "cycle of activity" to this class of phenomena. They plainly militate against the doctrine of "specific" disease germs held by Cohn and Koch, and they help us to understand one important thing concerning the production of disease, namely that it is not the transferable "essence" that determines the character of the "specificity" of disease, but the similarity and the permanency of the conditions of life. Since disease germs, presumably "specific," are able also to cause fermentations and to form pigments, it is clear that a close relation exists between the "parasitic" bacteria occurring in living human beings and the so-called "saprophytic" bacteria, the bacteria of putrefaction, which are able to live outside of the human body upon dead, lifeless, organic or inorganic material. Such relations are sometimes very easily traced, but are often obscure and in other cases are wanting. The parasitic organisms may accordingly be separated into obligatory parasites, facultative saprophytes, and facultative parasites.

In the first class the relations to processes of putrefaction, and the ability to live at the cost and by the destruction of lifeless food material, have gradually been completely lost, or at least such relations have up to the present not been made out. In this group may belong perhaps the yet undiscovered germs of the so-called acute exanthemata like smallpox, scarlet fever and measles, and also the germ already discovered, in relapsing fever. The facultative saprophytes are those germs that we find as a rule living as parasites, but which, under special conditions, maintain themselves also

upon lifeless material, and by breaking down this lifeless nutrient substance are able to grow, multiply and perpetuate the species. The saprophytic condition has been brought about in the case of the tubercle bacillus by Koch and by Fischel, one of my pupils, and I was able to show that this organism, which up to that time had been called tubercle bacillus, is only a parasitic form of a pleomorphic microbe, the other forms of which make their appearance only in the course of its saprophytic existence and were hence entirely overlooked at first. The group of facultative parasites comprises those species which can maintain and reproduce themselves in a purely saprophytic way upon lifeless material without ever necessarily attacking living hosts as parasites; indeed to attain certain stages of development it is necessary that they should live the life of real saprophytes. To this group belong the majority of the disease-producing bacteria now known, such as the bacteria of anthrax, typhoid fever, and cholera.

Finally there are bacteria which in a strict sense never invade the living organism, but yet are dangerous and able to provoke disease. Many of the bacteria of putrefaction are able to generate out of lifeless nutrient substances poisons that act injuriously on human beings without the poison-forming bacteria themselves being directly involved. This may happen in the normal organism in intestinal putrefaction, a process which seems in itself to have become necessary as a result of adaptation. Such bacteria may be designated as œco parasites, and may be regarded as transition forms to the facultative parasites. The organism may also be affected through the removal of protective structures of the body by the action of putrefactive poisons, for example, the intestinal epithelium may be killed; these saprophytes may then enter into the dead tissues, and may even penetrate still farther into the body as for instance into the nearest lymph glands. The common bacterium of the large intestine, *B. coli communis*, can do this. There are found, furthermore, transition forms between the different groups of parasitic microbes, so that it is evident that we are not here dealing with rigid groups, but only with a division which enables us to

recognise more easily the characters important from a human standpoint.

In the process of putrefaction, a process which forms an absolutely necessary link in the cyclical course of matter, are found represented the fundamental phenomena of parasitism out of which by development and adaptation to living hosts the various stages of parasitism have arisen. Putrefaction may exert in other respects an important influence upon the excitation of disease; volatile or soluble poisons of putrefaction may weaken the living organism so that it can be attacked more easily and successfully by the true parasites or by their toxins. The simple vegetation of certain saprophytes acts in such a way that disease germs following in their wake can get lodgment upon man the more readily, while on the other hand other saprophytes may hinder the lodgment of pathogenic organisms. Among the various possible effects thus wrought by saprophytic microbes outside and inside a living host must be included those that either favor or hinder the lodgment and action of the disease germs. That is to say these microbes act upon the disposition towards disease. They present therefore only individual cases, albeit particularly difficult to estimate, of external relations or of conditions which may now exalt an existing disposition to disease, now diminish it or remove it altogether.

This explanation should make it no longer difficult for the reader to understand the very various modes of action of disease-germs in man, since these possibilities of action have developed out of two activities already manifested in the process of putrefaction, namely out of the formation of poisons by bacteria, and out of bacterial growth and multiplication. At one extreme, therefore, we find a kind of parasitic action in which not the bacteria themselves but the poisons formed by them and absorbed into the circulation are the more important factors, while upon the other side stand those parasites which act especially through the formation of local growths or tumors. To the latter class belong the germs causing tumors which have been investigated with especial accuracy among plants, and a well-known example of which is the germ of human tuberculosis; to the former belong the germs of diphthe-

ria and tetanus; cholera also approximates to the former group. Between these extremes stand the other pathogenic bacteria: in some the proliferation of the bacteria, in others their production of poison is the predominant factor. Disease producing bacteria may therefore affect man in very different ways. By growing and multiplying in vital organs they may cause changes, and by thus altering the metabolism of important organs may influence unfavorably the metabolism of the whole body; or they may rob the body of important nutrient material and introduce the products of their own metabolism into the body of their host; or they may, in the act of satisfying their own need of energy, split off from the proteids of the human body certain substances which act upon man as poisons; or they may themselves generate poisons in their own bodies and like poisonous plants, be in themselves poisonous. The mode of action may vary according to conditions; for example, ergot is a local growth for the grain, a poison for man.

In all cases, from the simple germs of putrefaction and the œco-parasites up to the obligatory parasites, one thing is a prerequisite to successful invasion, namely, that as compared with the mechanical or chemical attacking powers of the microbe the mechanical and chemical resisting powers of man be relatively feeble or impaired. If this is not the case the human organism either does not allow the germ to gain entrance to the body, or when entrance is effected it nullifies the poisonous action by a counteraction.

After what has now been stated no particular assurance is necessary that bacteria and other minute pathogenic organisms do not exercise their injurious effect upon man from an inbred wickedness and pleasure in doing mischief, but that in the phenomena of parasitism we have to do simply with questions of adaptation, with the utilisation of situations, so to speak, which man himself provides by his own sins of hygienic omission and commission, and which therefore he himself is able to remove. The germs of putrefaction dispose of the dead bodies of all organisms in nature, simply to satisfy their own need of energy and the conditions of their own metabolism. This is also the case when they adapt themselves

to the conditions of intestinal putrefaction. They may for the same reason invade the living organism whenever its normal protecting power has become enfeebled through errors in hygiene.

The second question is, Do the so-called "specific" disease germs vary in their capacity to produce disease? Buchner was the first to succeed, upon the basis of systematic experiments, in proving that the so-called anthrax bacilli can be influenced artificially in such a way that they can no longer bring about any illness, but behave like perfectly harmless saprophytes. The same discovery was soon afterwards made accidentally by Pasteur in regard to the bacteria of so-called chicken cholera, and we now know from hundreds of experiments that no peculiarity of disease-producing bacteria is more easily affected than the very capacity in question, commonly presumed to be "specific," of producing disease. The physician who seeks the "essence" of the disease in the "specificity" of the disease germs can plainly attach importance only to those parasites whose "specific" capacity of producing disease is invariable. The facts that demonstrate the variability of this capacity therefore obviate all need for seeking an "essence."

The third question is this: Do the same "specific" disease germs affect all animals with the same typical disease? This question must also be answered in the negative. We see that each kind of disease germ affects only certain hosts; syphilis, leprosy, cholera, and typhoid fever, are known only in man, while tuberculosis, glanders, and anthrax, attack both man and certain kinds of animals.

The fourth question is whether a "specific" disease germ causes only one disease. We may distinguish in this inquiry two groups of phenomena. In the first group belong those facts showing that similar symptoms may be evoked and that the same organs or tissues may suffer anatomically similar changes through the action of entirely different germs. For example, the formation of nodules or tubercles in connective tissue may be brought about by the germs of syphilis, leprosy, glanders, and tuberculosis; suppuration can be caused by the germs of wound erysipelas, the tubercle bacilli, the anthrax bacilli, and the germs of typhoid fever and

pneumonia; both the common bacteria of the colon and the cholera bacteria can incite diarrhœa; the bacteria of tuberculosis, of typhoid fever and pneumonia may produce inflammation of the pia mater; tubercle, typhoid, and pneumonia bacteria, gonococci, staphylococci, and streptococci, may cause endocarditis; the phenomena of blood-poisoning are caused by a whole series of bacteria. In these cases, therefore, the determining cause resides in the tissues and their disposition, not in the entirely distinct kinds of bacteria.

The second group of facts, belonging with these but obtained in another way, demonstrate that one and the same "specific" disease germ may produce very different affections. Diphtheria bacteria, for example, may occasion local diphtheria or paralysis or acute blood-poisoning; the bacteria of erysipelas may bring about erysipelas in the skin, but are able also to produce suppuration or inflammation of the lungs; the pneumonia germs may cause typical pneumonia, blood-poisoning, inflammation of the cerebral membranes, or inflammation and suppuration of the middle ear; tubercle bacilli excite tubercle formation in connective tissue, inflammation of the cerebral membranes, suppuration and true consumption or phthisis.

Perhaps still a third group might be added, comprising the critical diseases like intermittent fever, relapsing fever and pneumonia. Many observers suppose, in accord with Henle, that the germs of these diseases in man have a course of development sharply defined by hours or days, and that therefore the life-cycle of the germ determines the cycle of the disease. So far, however, as we know anything about these germs, we never find such remarkable cycles occurring outside of the human body. The pneumonia germs cause crises only in man, while in rabbits they bring about simple blood-poisoning without any cycle. In cultures they show no regular cyclical character at all. For these reasons I am inclined to seek the basis of such activity of a cyclical nature in peculiarities of the human organisation, and the more so that even in man pneumonia may sometimes occur without crisis and show a resemblance to forms of blood-poisoning.

Upon sifting all the available material, I cannot find a fact which is in real harmony with Koch's conception of "specific" disease-germs. I must protest also against the view held by Billroth and Naegeli, which is extreme and one-sided and I expressly acknowledge that we can distinguish species and genera among bacteria and other minute organisms. Such constancy as we observe, however, is not the mystical constancy of "specific" essences, but a constancy made possible by the permanence of the environment. The organisms change with the changes in their surroundings, and the placing of this fact on a sure footing constitutes the great advance that modern bacteriology has made beyond the standpoint reached by Koch.

Just as the human being possessed of a definite organisation is compelled continually to adapt himself to changing conditions of life, so is the microbe also constrained to the same task. In the majority of men the bodily constitution is always oscillating, manifesting now increase, now decrease of a definite disposition toward disease. The microbes also vary according to the conditions imposed upon them and display increased or decreased capacity to grow or form poisons in the human body, capacity in other words to remove with greater or less difficulty the resistance inherent in the human organisation. Accordingly we observe the occurrence of both mild and severe epidemics, and in every epidemic, along with the "typical" cases, we find especially grave or especially light cases which do not conform to the schema.

If we diminish the disposition of a man toward a disease we influence his organisation in the sense of exalting its resistance to infection. In this way the same effect is produced as when we diminish the "contagious" or toxic quality of the disease germ, the disposition of the man to the disease remaining the same. The ordinary anthrax bacteria, for example, cause in guinea-pigs a generalised blood-poisoning which is speedily fatal, and in dogs, which are naturally immune towards this disease they cause at most an abscess, or a local suppuration. But if we diminish to a certain extent the disease-producing power of the anthrax bacilli, they pro-

voke in the otherwise very susceptible guinea-pig merely a local suppuration which readily heals.

The disease germs remaining the same, it is possible to heighten natural predisposition to disease by starving animals, or chilling them, or modifying their metabolism unfavorably by inducing artificial diabetes. In such cases animals succumb to the very disease germs against which when in a normal healthy condition they are immune. We know also that through hunger, insufficient nutriment, and disorders of metabolism such as diabetes, human beings are rendered more easily susceptible to infection than when in a sound and normal condition. Before the days of antiseptics the "healthy skin" played an important part in the progress of a wound.

The "specific" qualities of disease germs, qualities which they possess as do all living things adapted or adapting themselves to definite conditions of life, can only become manifest in the shape of a specific infectious disease when the forms of motion which they impart in order to overcome the resistances arising from the organisation of the human body happen to accord with the possibilities of motion which occur in the structure of man as the result of inheritance and adaptation. Only in this way is it possible to account for the fact that—as has been proved concerning some moulds—micro-organisms which, so far as we know, occur only as saprophytes upon dead material are able to produce disease when for the first time,—thus excluding any possibility of an adaptation,—they are artificially inoculated into susceptible animals.

If the facts are considered in a scientific spirit, rigorously and without prepossession, it is seen that the sum of the qualities of a disease germ is only apparently the "essence" of an infectious disease, that in reality, here as elsewere, a true internal cause is to be found, inherent in the internal organisation of man. Just as in all natural processes without exception, so here the disease germs act as liberating impulses and are able to set free only what in the form of a predisposition toward disease is in some way prefigured both in nature and amount in the human body.

The dependence of both resistance and disposition to disease

upon the conditions of life, as well as a like dependence of the disease germs upon their conditions of existence—inasmuch as they likewise are living organisms—explains, without recourse to violent assumptions, such facts as that insignificant local infectious diseases may become world-wide, as cholera has done in our own century, that new infectious diseases may make their appearance, as for instance cerebro-spinal meningitis in the last hundred years, and that diseases once widely spread like leprosy and the bubonic plague may dwindle almost to the vanishing-point. We can easily understand the fact also that everywhere, even under conditions originally very different, similar cultural influences arising from similar unsanitary social conditions lead everywhere to the same danger from diseases such as tuberculosis, for the reason that such conditions create a larger number of the same or similar dispositions towards disease.

That the "specificity" of the disease germs is a phenomenon of adaptation, and hence not an essence is manifest also from the fact that the parasites adapt themselves to given conditions of life not only in their mode of action but in their form. Koch has shown that the anthrax bacteria develop their characteristic form of rods only in their parasitic phase. The tubercle bacilli have such a strongly marked capacity of adaptation that Maffucci and Koch even distinguished as separate species or varieties the germs of mammalian tuberculosis. Fischel and Hueppe, however, by the choice of suitable parasitic and saprophytic conditions of life succeeded in converting the two kinds one into the other, and thus in proving that it is similarity or difference in conditions which ultimately brings about such great divergence.

Finally, in other cases of which more accurate studies were made long since, especially among the higher animal and plant parasites, a close adaptation to the conditions of life is manifested in the fact that a parasite, in order to complete its development, needs not only an interchange of parasitic and saprophytic modes of life, like the facultative parasites among bacteria, but requires a complete and more or less extensive alteration of generations. Such a parasite, in other words, attacks different animals and plants one

after another, in each of which it passes through a definite stage of development.

Among most parasites there occurs a free or saprophytic stage which is advantageous to the maintenance of the species. In such a case the parasite is often autœcious, that is, no change of host occurs. In alternation of generations there is always change of host or heterœcism, so that in the extreme cases of strongly obligatory parasitism this occurs in a fashion as if saprophytism were altogether omitted. In the tape-worm, for example, we know no free stage; the eggs pass into the outer world but do not develop (at least up to the present nothing of the sort is known). The scolex of *Tænia solium* is found in hogs, the tape-worm in man; the scolex of *Tænia mediocanellata* is found in cattle, the tape-worm belonging to it in man; the Echinococci are found in man, the respective tape-worm in dogs. The scolex of *Bothriocephalus latus* is found in predaceous fishes, and the tape-worm in man, but free living embryos arise from the eggs in water. In this latter case, therefore, a limited free stage does occur. In *Distomum hepaticum* three parasitic and two free stages are known.

We know that among the rusts or Uredineæ there occur upon grain summer spores or uredospores (stylospores) and winter spores or teleutospores; out of the latter are formed saprophytically in the fallen leaves a promycelium which develops sporidia; these get lodgment upon the barberry leaf in which the æcidia develop and form besides spermogonia, the so-called spermatia. We have therefore three to four parasitic forms and one free form. Among the smuts or Ustilagineæ the mycelium develops spore-bearing filaments upon the grain; out of these spores a promycelium with spiridia is formed saprophytically; the sporidia may invade young plants and so begin again the parasitic cycle, but they are able also to vegetate saprophytically for countless generations in a torula form. Here two saprophytic forms and one parasitic form are able to exist. The spores of most vegetable parasites are able to develop either a saprophytic form or another parasitic form.

An alternation of generations of this kind has not yet been demonstrated among disease-producing bacteria and other microbes,

but with some species its existence is not wholly improbable. It is obvious that such complications increase the difficulty of research, already arduous, but the fundamental facts that have been discussed are not thereby affected or in any way altered. The body of living organisms offers relatively constant conditions, and that explains why, in spite of the complexity due to an alternation of generations in several hosts, the parasites can remain relatively the same.

INFECTION AND CONTAGION.

I cannot conclude my examination into the causes of infectious disease without referring to still another feature of the external conditions which may be very important practically. Granting the existence of a given disposition toward disease, disease germs can evidently afford opportunity for the manifestation of this disposition only when they come in contact with it. That is the broad meaning of the word infection. From this point of view, accordingly, the unsuitable condition of the general surroundings of life, such as air, water, soil, and nourishment, may be of importance by virtue of being the means by which the disease germ is first introduced into us. The quite various channels of the mouth, the lungs, and the skin are available for entrance. The organs affected in an infectious disease are sometimes in the place where the disease germ enters, sometimes in tissues remote but more disposed toward the disease; the expression *locus minimæ resistentiæ* is a designation used to denote their relation.

From this standpoint we classify those diseases as contagious which can be directly communicated by mere contact with the sick and do not need a go-between; and as miasmatic or non-contagious those which are not transmitted directly from the sick but are caused by external agents. In the great majority of infectious diseases both possibilities of communication exist; one or the other is the more usual merely. In this sense malaria is never naturally contagious, but may be artificially communicated by transfusion of blood; cholera is generally not contagious; small-pox is always contagious. The concept contagion is accordingly used in a nar-

rower sense than that of infection, and if we depart from this general usage we must always declare the fact and make it abundantly evident. I say this expressly because certain bacteriologists use the term contagion to express the same conception as that implied in the term infection or wound infection. If this is done in the face of usage, of the clinical experience of physicians and of the experience of every layman, then naturally all diseases must be called contagious, for the word used in this fashion loses completely its peculiar and narrower significance. By some such quibble, for example, Koch and certain of his followers are able to declare cholera to be a contagious disease, while medical experience as well as bacteriological experiments prove plainly that cholera as a rule is not in the strict sense a contagious disease.

FERDINAND HUEPPE.

PRAGUE.